REMARKS/ARGUMENTS

The specification stands objected to with regard to the priority claim, and amendment to indicate the proper relationship between the applications being claimed under 35 U.S.C. §120 has been required. As amended, the priority claim recites the relationship between the applications being claimed under 35 U.S.C. §120.

The amendments to Claim 124 find support in the specification and claims as originally filed. For example, support for the phrase "wherein a disulfide bridge is avoided by substituting another amino acid for the corresponding cysteine residue in the opposite chain of said antibody fragment" may be found in the specification, for example, at page 51, lines 4-6 and 10-12; page 56, lines 1-2, 10-11, 19-20, and 27-28; page 66, lines 23-24; page 68, lines 20-21; and elsewhere in the specification.

Support for the phrase "the conjugate has an apparent size that is at least about 8-fold greater than the apparent size of the parental antibody fragment" may be found in the specification, for example, at page 44, lines 21-22 and 26; page 45, lines 1-3; and elsewhere in the specification.

Support for new Claim 133 may be found in the specification and claims as originally filed. In particular, support for new Claim 133 may be found at page 41, lines 17-23; page 48, lines 3-9; and page 51, lines 1-6; and page 53, lines 9-16 *et seq.*; and elsewhere in the specification.

No new matter is added by way of the amendments to the specification or by way of the claim amendments and the new claim.

Claims 124-132 are pending in the application. Claims 124-132 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly obvious over Claims 1, 20, 25, 26, 28, 31, and 32-36 of copending U.S. Patent Application Serial No. 09/726,258 in view of Carter et al. (Antibody Engineering, A practical approach, IRL Press, chapter 13, pages 291-308 (1996), hereafter "Carter") and Allan et al. U.S. Patent No. 5,620,689 (hereafter "Allan"). Claims 124-132 stand rejected under the judicially created doctrine of obviousness-type double patenting as allegedly obvious over Claims 1 and 27 of copending U.S. Patent Application Serial No. 09/35,014 in view of Carter and Allan. Claims 124-130 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over U.S. Patent No. 6,133,426 to Gonzalez et al. (hereafter "Gonzalez") in view of Zapata et al. (FASEB J. **9**:A1476 (1995), hereafter "Zapata"). Claims 124-130 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over U.S. Patent No. 5,695,760 to Faanes et al. (hereafter

"Faanes") in view of Zapata and U.S. Patent No. 5,766,897 to Braxton et al. (hereafter Braxton). Claims 124-132 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Faanes in view of Zapata and Braxton and further in view of Carter and Allan. Claims 124-132 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Koumenis at al. (*Protein Science* **7(suppl. 1)**:73 (1998), hereafter "Koumenis") in view of Carter and Allan.

Priority

The amendments to the priority claim indicate the relationship between the applications named in the priority claim and the present application: the present application is a continuation-in-part of copending U.S. Patent Application Serial Nos. 09/355,014, 09/012,116, and 09/026,985 named in the priority claim. The amended priority claim also recites that U.S. Patent Application Serial No. 09/355,014 is a continuation-in-part of U.S. Patent Application Serial No. 08/804,444, now U.S. Patent No. 6,117,980.

Accordingly, Applicants submit that the specification indicates the proper relationship between the applications claimed under 35 U.S.C. §120, and respectfully submit that the objection to the specification is overcome.

The Examiner further suggests that U.S. Patent Application Serial Nos. 09/355,014; 08/804,444; 09/012,116; 09/026,985, 60/038,664; and 60/074,330 all lack support for a conjugate of an antibody that binds VEGF, HER2, CD20, CD18, CD11a, human IgE, human Apo-2 receptor, TNF-α, TF, human integrin, EGFR, CD3, and TAC. Such alleged lack of support is cited in discussion relating to the Examiner's denial of priority back to the earliest priority date of the applications from which priority is claimed. However, the present claims, as amended, do not recite a conjugate of an antibody that binds VEGF, HER2, CD20, CD18, CD11a, human IgE, human Apo-2 receptor, TNF-α, TF, human integrin, EGFR, CD3, and TAC. Thus, whether or not there is support for such claim elements is believed to be moot and not relevant to the priority of the present application.

Applicants note that support for the present claims is found in the patent issued from U.S. Patent Application Serial No. 09/026,985, filed February 20, 1998 (now U.S. Patent No. 6,133,426) which claims priority to U.S. Provisional Application Serial No. 60/038,664, filed February 21, 1997. Support is found, for example, at column 15, lines 24-40; column 16, lines 26-34; column 19, lines 55-60; column 20, lines 3-12, and elsewhere in U.S. Patent No. 6,133,426.

Accordingly, support for the present claims being found in the present application and in priority applications having filing dates beginning February 21, 1997, Applicants submit that the earliest priority date for the claims of the present application is February 21, 1997.

The "Double Patenting " Rejections of Claims 124-132 over Claims 1, 20, 25, 26, 28, 31, and 32-36 of 09/726,258 in view of Carter and Allan

Claims 124-132 stand provisionally rejected under the judicially created doctrine of obviousness double patenting over Claims 1, 20, 25, 26, 28, 31, and 32-36 of U.S. Patent Application Serial No. 09/726,258 in view of Carter and Allan.

In order to expedite prosecution of the present claims to issue, and without acquiescing to the rejections, Applicants have filed a Terminal Disclaimer over U.S. Patent Application Serial No. 09/726,258. Accordingly, Applicants believe that the rejections of Claims 124-132 under the judicially created doctrine of obviousness double patenting over Claims 1, 20, 25, 26, 28, 31, and 32-36 of U.S. Patent Application Serial No. 09/726,258 in view of Carter and Allan are overcome.

The "Double Patenting " Rejections of Claims 124-132 over Claims 1 and 27 of U.S. Patent Application Serial No. 09/355,014 in view of Carter and Allan

Claims 124-132 stand provisionally rejected under the judicially created doctrine of obviousness double patenting over Claims 1 and 27 of U.S. Patent Application Serial No. 09/355,014 in view of Carter and Allan.

In order to expedite prosecution of the present claims to issue, and without acquiescing to the rejections, Applicants have filed a Terminal Disclaimer over U.S. Patent Application Serial No. 09/355,014. Accordingly, Applicants believe that the rejections of Claims 124-132 under the judicially created doctrine of obviousness double patenting over Claims 1 and 27 of U.S. Patent Application Serial No. 09/355,014 in view of Carter and Allan are overcome.

The Rejections Under 35 U.S.C. §103(a) over Gonzalez in view of Zapata

Claims 124-130 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Gonzalez in view of Zapata.

As discussed above, Gonzales is not a proper reference since it is a co-pending application to which priority has been properly claimed. Accordingly, Gonzalez et al. not being a proper reference, the rejection of Claims 124-130 under 35 U.S.C. §103(a) as allegedly being obvious over Gonzalez in view of Zapata is reduced to being a rejection of Claims 124-130 under 35 U.S.C. §103(a) as allegedly being obvious over Zapata.

In order to establish a prima facie case of obviousness, there must be: 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Zapata discusses anti-CD-18 Fab' antibody fragments to which either a 5 kD or a 10 kD monomethoxypoly(ethylene glycol) (MePEG) was attached. The single MePEG was attached to the single free thiol of the anti-CD-18 Fab' antibody fragment. No anti-CD-18 Fab' antibody fragments were made having two attached MePEG molecules. However, Zapata fails to discuss many elements of the claimed invention. For example, Zapata fails to discuss an antibody conjugate having any nonproteinaceous polymer molecules with an average actual molecular weight of at least 20 kD. Zapata also fails to discuss a conjugate with an apparent molecular weight of at least about 500 kD; fails to discuss substitution of any amino acid residues in the opposite chain of the antibody fragment in order to avoid formation of a disulfide bridge; and fails to discuss a conjugate that has an apparent size that is at least about 8-fold greater than the apparent size of the parental antibody fragment.

Thus, Zapata does not provide all the elements of the claimed invention.

Moreover, there is no suggestion or motivation to provide these missing elements. Lacking discussion of nonproteinaceous polymer molecules of any size greater than 10 kD, there is no suggestion or motivation to provide conjugates having nonproteinaceous polymer molecules with average molecular weights of at least 20 kD. Lacking discussion of any substitutions of any amino acid residues in the opposite chain of the antibody fragment, and lacking discussion of such substitutions in order to avoid formation of a disulfide bridge, there is no motivation or suggestion to provide conjugates having these features. Lacking discussion of the apparent size of an antibody or of an antibody-MePEG conjugate, Zapata fails to suggest or to motivate one of ordinary skill in the art to provide a conjugate that has an apparent size that is at least about 8-fold greater than the apparent size of the parental antibody fragment.

Failing to discuss at least these elements, and failing to suggest them, or to motivate one of ordinary skill in the art to provide these elements, Zapata also fails to provide any reasonable expectation of success for such a combination of elements, even if one were (with hindsight) to provide all these elements.

Accordingly, Applicants respectfully submit that the rejections of Claims 124-130 under 35 U.S.C. §103(a) as allegedly being obvious over Gonzalez in view of Zapata are overcome.

The Rejections Under 35 U.S.C. §103(a) over Faanes in view of Zapata and Braxton

Claims 124-130 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Faanes in view of Zapata and Braxton.

Zapata has been discussed above. Faanes is presented by the Examiner as discussing methods and modifications of antibodies and antibody fragments with attachment of PEG molecules to the antigen binding fragments, and as discussing anti-CD 18 antibodies, humanization, fragments, including fragments modified to contain about 2-15 molecules of PEG, and as discussing "that adding PEG to an antibody leads to an increased apparent molecular weight as taught on column 19, lines 23-41" (Office action dated September 27, 2004, page 6, lines 2-3). Braxton is presented by the Examiner as discussing methods for PEGylating proteins by attaching a PEG molecule via the thiol on a free cysteine, and as discussing that the molecular weight of the attached PEG may be from 0.2 to 20 kD.

Faanes discusses the use of antibody PEGylation in order to reduce the immunogenicity of a PEG-derivatized antibody in an animal. For example, Faanes discusses PEGylation of full-length anti-ICAM antibody with 5 kD PEG at, *e.g.,* column 21-23. However, out of 17 exemplified conjugates, only 3 were found to have reduced immunoactivation in immunized animals as compared to the underivatized antibody; these three were not characterized as to possible shared structural features, although the use of 5 kD PEG is referred to as "preferred" throughout the disclosure. Thus, discussing 5 kD as preferred, and providing no suggestion of an apparent molecular weight of at least about 500 kD, Faanes provides no motivation for one skilled in the art to prepare conjugates with an apparent molecular weight of at least about 500 kD.

Braxton discusses PEG molecules attached to proteins; the proteins are not identified as possibly being antibodies. As discussed above, Braxton discusses PEG molecules of a molecular weight of between 0.2 kD and 20 kD, that is, of at most 20 kD. Accordingly, Braxton provides no suggestion or motivation to conjugate PEG molecules of at least about 20 kD to antibody fragments to obtain antibody fragment conjugates having an apparent molecular weight of at least about 500 kD.

In addition, Applicants note that Faanes and Braxton each fails to discuss many elements of the claimed invention. For example, neither Faanes nor Braxton teach a conjugate in which the apparent molecular weight of the conjugate, as determined by size exclusion

chromatography, is at least about 500 kD. Neither Faanes nor Braxton discuss antibody fragment-polymer conjugates having an apparent size that is at least about 8-fold greater than the apparent size of the parental antibody fragment.

Moreover, as noted by the Examiner, "Faanes does not teach attachment of PEG to the hinge region of the antibody fragment or that the PEG is specifically 20 kD" (page 10, lines 11-12 of the instant Office Action). Braxton also fails to discuss attachment of a non-proteinaceous polymer to a hinge region of an antibody or antibody fragment.

Faanes and Braxton each also fails to teach attachment of PEG, or any other non-proteinaceous polymer, to an antibody fragment in which a disulfide bridge was avoided by substituting another amino acid for the corresponding cysteine residue in the opposite chain of said antibody fragment.

As discussed above, Zapata, discussing 5 kD and 10 kD molecules, does not suggest the use of larger molecular weights; Faanes discusses 5 kD PEG conjugates; and Braxton discusses conjugates with PEG having a molecular weight of up to 20 kD. None of the cited references discuss antibody fragments conjugated with non-proteinaceous polymer molecules of at least about 20 kD and having an apparent molecular weight of at least about 500 kD.

In addition, failing to discuss a hinge region of an antibody or an antibody fragment, and failing to discuss an antibody fragment in which a disulfide bridge was avoided by substituting another amino acid for the corresponding cysteine residue in the opposite chain of said antibody fragment, the cited references are lacking discussion of many elements of the claimed invention.

Thus, even if combined together, the combination of Faanes, Zapata, and Braxton lacks at least the following elements of the claimed antibody fragment conjugates:

an apparent molecular weight of at least about 500 kD;

an apparent size that is at least about 8-fold greater than the apparent size of the parental antibody fragment;

a non-proteinaceous polymer attached to a hinge region of an antibody or antibody fragment; and

having a cysteine available for conjugation by substituting another amino acid for the corresponding cysteine residue in the opposite chain of a disulfide bridge that would otherwise have been present in the antibody fragment.

The cited references not only fail to discuss at least these elements, the cited references provide no suggestion or motivation to provide them. Thus, the cited references fail to discuss and fail to provide any suggestion of at least these elements of the claimed

invention. Failing to suggest at least these elements, the cited references provide no motivation to be combined to provide the claimed invention. Failing to provide at least these elements, and failing to provide motivation to combine the references in an attempt to provide the claimed invention, the cited references fail to provide a reasonable expectation of success for such a combination.

Accordingly, Applicants respectfully submit that rejections of Claims 124-130 under 35 U.S.C. §103(a) as allegedly being obvious over Faanes in view of Zapata and Braxton are overcome.

The Rejections Under 35 U.S.C. §103(a) over Faanes in view of Zapata, Braxton, Carter and Allan

Claims 124-132 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Faanes in view of Zapata and Braxton and further in view of Carter and Allan.

Faanes, Zapata, and Braxton have been discussed above, the combination of which lacks at least the elements of antibody fragment-non-proteinaceous polymer conjugate having an apparent molecular weight of at least about 500 kD, an apparent size that is at least about 8-fold greater than the apparent size of the parental antibody fragment, a non-proteinaceous polymer attached to a hinge region of an antibody or antibody fragment; and a cysteine available for conjugation by substituting another amino acid for the corresponding cysteine residue in the opposite chain of a disulfide bridge that would otherwise have been present in the antibody fragment.

Carter is presented by the Examiner as discussing a conjugate of PEG to an anti-HER2 antibody, and Allan is presented by the Examiner as discussing a conjugate of PEG to an anti-CD20 antibody.

However, as amended, Claims 124-132 do not recite an anti-HER2 antibody nor do they recite an anti-CD20 antibody. Moreover, neither Carter nor Allan provide any of the missing elements lacking in the combination of Faanes, Zapata, and Braxton, nor do Carter and Allan provide any suggestion or motivation to provide these missing elements. Carter and Allan together fail to make obvious the claimed invention, and Carter and Allan together also fail to make up the deficiencies of the other cited references. Thus, even if combined, Faanes in view of Zapata and Braxton and further in view of Carter and Allen fail to provide or to suggest all the elements of the claimed invention.

Failing to suggest at least these elements, the cited references provide no motivation to be combined to provide the claimed invention. Failing to provide at least these elements, and

failing to provide motivation to combine the references in an attempt to provide the claimed invention, the cited references fail to provide a reasonable expectation of success for such a combination.

Accordingly, Applicants respectfully submit that the rejections of Claims 124-132 under 35 U.S.C. §103(a) as allegedly being obvious over Faanes in view of Zapata and Braxton and further in view of Carter and Allen are overcome.

The Rejections Under 35 U.S.C. §103(a) over Koumenis in view of Carter and Allan

Claims 124-132 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Koumenis in view of Carter and Allan.

Koumenis is presented by the Examiner as discussing a Fab' modified with PEG of molecular weight of 20 and 30 kD and hydrodynamic volumes of 300 kD to 2 million kD, with no loss of bioactivity, the Examiner suggesting that the study allegedly demonstrated the importance of higher molecular weight PEG at fewer sites. Carter and Allan are presented by the Examiner as discussed above.

Koumenis was published in July 1998. The priority of the present application is February 21, 1997, the filing date of the provisional application from which U.S. Patent No. 6,133,426 claims benefit (and, incidentally, also after the filing date of the patent itself, February 20, 1998). Thus, Koumenis is not a proper reference, being filed after the priority date of the present application.

Carter and Allan have been discussed above. Neither Carter nor Allan provide the elements of antibody fragment-non-proteinaceous polymer conjugate having an apparent molecular weight of at least about 500 kD, an apparent size that is at least about 8-fold greater than the apparent size of the parental antibody fragment, a non-proteinaceous polymer attached to a hinge region of an antibody or antibody fragment; and a cysteine available for conjugation by substituting another amino acid for the corresponding cysteine residue in the opposite chain of a disulfide bridge that would otherwise have been present in the antibody fragment.

Moreover, even were Koumenis a proper reference, it also lacks discussion or suggestion of attachment of a nonproteinaceous polymer molecule to a free sulfhydryl group of a cysteine residue within the hinge region of an antibody fragment, and a cysteine available for conjugation by substituting another amino acid for the corresponding cysteine residue in the opposite chain of a disulfide bridge that would otherwise have been present in the antibody

fragment. As discussed above, lacking these elements themselves, neither Allan nor Carter provide the missing elements.

Thus, even if combined, Koumenis, Carter and Allan fail to provide all the elements of the claimed invention, and fail to suggest all the elements of the claimed invention.

Accordingly, Koumenis not being properly a prior art reference against the present application, Carter and Allan failing to provide the elements of the claimed invention, and the combination of these references failing to provide suggestion or motivation to provide the claimed invention, these references do not properly provide any suggestion or motivation to be combined to provide the claimed invention. In addition, lacking any disclosure or suggestion, even if combined, of elements of the claimed invention, the combination of these references provides no reasonable expectation of success for the claimed invention. Failing to provide all the elements, failing to motivate or suggest the combination of the references, and failing to provide a reasonable expectation of success for the claimed invention, Applicants respectfully submit that the rejections of Claims 124-132 under 35 U.S.C. §103(a) as allegedly being obvious over Koumenis in view of Carter and Allan are overcome.

CONCLUSION

In conclusion, Applicants respectfully submit that all claims are in condition for allowance, and request reconsideration and allowance of all pending claims.

The Examiner is invited to contact the undersigned attorney at the telephone number indicated below should he find that there are any further issues outstanding.

Please charge any fees, including fees for extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No. **39766-0092 A**.

Respectfully submitted,

Date: February 14, 2005

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